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(54) Title: TRANSDERMAL DRUG DELIVERY DEVICE FOR THE DELIVERY OF TROPISETRON OR GRANISETRON

(57) Abstract

The present invention discloses a transdermal drug delivery device comprising on a backing an adhesive layer, said adhesive layer comprising: (a) a copolymer of one or more A monomers and one or more B monomers, said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said (B) monomers being hydrophilic monomers copolymerizable with said (A) monomers, and (b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron. The transdermal drug delivery device is suitable for the treatment of emesis and/or nausea or for the prevention of emesis and/or nausea. Further provided are pressure sensitive skin adhesives containing tropisetron or granisetron.

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DESCRIPTION

TRANSDERMAL DRUG DELIVERY DEVICE FOR THE DELIVERY OF TROPISETRON OR GRANISETRON

1. Field of the invention.

The present invention relates to a transdermal drug delivery device for the delivery of tropisetron or granisetron.

2. Background of the invention.

Transdermal drug delivery devices are designed to deliver a therapeutically effective amount of drug across the skin of a patient. Transdermal drug delivery devices typically involve a carrier (such as a liquid, gel, or solid matrix, or a pressure sensitive adhesive) into which the drug to be delivered is incorporated. Devices known to the art include reservoir type devices involving membranes that control the rate of drug release to the skin and devices involving a dispersion of the drug in a matrix such as a pressure sensitive adhesive. The skin, however, presents a substantial barrier to ingress of foreign substances into the body. It is therefore often desirable or necessary to incorporate certain materials that enhance the rate at which the drug passes through the skin.

It is known that the delivery of drugs across the skin avoids hepatic first-pass inactivation, poor or erratic absorption from gastro-intestinal tract, inactivation by gastro-intestinal fluids, and other modes of inactivation characteristic of oral drug ingestion. However, the type of device, suitable components for use in the device, the transdermal flux rate that is suitable, and the suitable formulation components are dependent upon the particular drug to be delivered.

Tropisetron (endo-1H-Indole-3-carboxylic acid 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester) and granisetron (endo-1-Methyl-N-(9-methyl-9-aza-bicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide) are drugs that are structurally very similar. Both are known to be specific serotonin ($5\text{-}HT_3$) receptor antagonists and both are known to be useful as anti-emetics and are of particular use to treat and prevent emesis during chemotherapy. In such therapy, they are typically administered by injection which is uncomfortable for a

patient. Other known medical indications of these drugs include their use as anti-nausea treatments.

WO 96/8229 discloses transdermal drug delivery devices that comprise a macromer containing (meth)acrylate adhesive layer containing a drug. Amongst the many drugs that are contemplated for use in the device there is mentioned ondansetron as an anti-emetic.

WO 94/07468 discloses a two-phase hydrophilic drug containing matrix for use in transdermal drug delivery patches in which one phase is a continuous hydrophobic polymer phase and the other phase is a dispersed particulate hydrated inorganic silicate in whose absorbed aqueous phase the drug is dissolved. Amongst the drugs mentioned are the anti-emetics ondansetron and granisetron.

3. Summary of the invention.

The present invention provides a transdermal drug delivery device comprising on a backing an adhesive layer, said adhesive layer comprising:

(a) a copolymer of one or more A monomers and one or more B monomers , said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said B monomers being hydrophilic monomers copolymerizable with said A monomers, and

(b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron.

The present invention further provides a pressure sensitive skin adhesive comprising :

(a) a copolymer of one or more A monomers and one or more B monomers , said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said B monomers being hydrophilic monomers copolymerizable with said A monomers, and

(b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron.

Still further, the present invention provides a transdermal drug delivery device as defined above for the treatment of emesis and/or nausea or for the prevention of emesis and/or nausea and the use of the pressure sensitive skin adhesive in the manufacture of a transdermal drug delivery device for use in the treatment or prevention of emesis or for use in the treatment or prevention of nausea.

4. Detailed description of the invention.

In accordance with the present invention it was found that the adhesive layer should include an acrylate or methacryate polymer that also includes a hydrophilic comonomer. It is believed that the latter comonomer provides the necessary solubility of the drug in the adhesive layer.

Hydrophilic B monomers in connection with the present invention are typically monomers that have a tendency to bind or absorb water and are preferably monomers of which a homopolymer shows a tendency to swell or dissolve in water. Examples of B monomers include N-vinyl-2-pyrrolidone, vinylimidazoles, 2-hydroxyethylacrylate, mono acrylates of poly(alkyleneoxide) alkyl ether, mono methacrylates of poly(alkyleneoxide) alkyl ether, acrylamides, methacrylamides, N-vinyl valerolactam, N-vinyl caprolactam, vinyl acetate, tetra-alkylammonium containing monomers such as (meth)acryloxyethyl trimethylammonium chloride, (meth)acryloxyethyl triethylammonium chloride, (meth)acrylamido-ethyl trimethyl ammonium chloride and aminogroup containing monomers such as dimethylaminoethyl(meth)acrylate, diethylamino(meth)acrylate, morpholino-ethyl(meth)acrylate, piperidino-ethyl(meth)acrylate, piperidino-ethyl-(meth)acrylamide, dimethylamino-ethyl(meth)acrylamide and diethylamino-ethyl(meth)acrylamide. Particularly preferred is N-vinyl-2-pyrrolidone.

Preferably, the B monomer is free of nucleophilic groups, in particular those that are capable of reaction with ester functions in the copolymer. While not intending to be bound by any theory, it is believed that such nucleophilic groups might react with ester functions in the copolymer leading to cross-linking of the adhesive layer and accordingly reducing the storage stability of the transdermal drug delivery device. Presumably, such reaction would be catalysed by the drugs which are fairly strong bases. For example, tropisetron has a pK_a of about 9.5. Preferably, the B monomer is free of nucleophilic

groups selected from the group consisting of hydroxy, thiol, primary amino groups, secondary amino groups and acid groups.

A monomers of the copolymer in the adhesive layer are alkylacrylate or alkylmethacrylate monomers containing 4 to 12 carbon atoms in the alkyl group. Examples of A monomers include n-butyl, n-pentyl, n-hexyl, cyclohexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, isobornyl, 2-ethyloctyl, isooctyl, n-octyl and 2-ethylhexyl acrylates and methacrylates.

The copolymer may further comprise units that are derived from monomers other than A and B monomers . Such monomers are preferably also free of groups containing nucleophilic groups as described above. Examples of other monomers that can be copolymerised with the A and B monomers include short chain alkyl acrylates and methacrylates such as ethyl(meth)acrylate and methyl(meth)acrylate and styrene.

According to a particularly preferred embodiment in connection with the present invention, the copolymer comprises units derived from a macromer that is copolymerizable with the A and B monomers . This offers the advantages that little or no adhesive remains on the skin after peeling a transdermal drug delivery device according to this invention from the skin, the cold flow of the adhesive composition is reduced and an improved cohesion of the adhesive composition can be obtained. The macromer preferably has a weight average molecular weight between 5000 and 500000 as measured by GPC relative to a polystyrene standard, more preferably between 2000 and 10000 and most preferably between 5000 and 30000. Examples of suitable macromers include those described in WO96/8229 and in particular include polymethylmethacrylate macromer, polymethylacrylate macromer, polystyrene macromer and polystyrene-acrylonitrile macromer.

Polymethymethacrylate macromers for use in this invention are commercially available under the trade designation "ELVACITE" by ICI Acrylics (e.g., ELVACITE 1010, a polymethylmethacrylate macromonomer having an inherent viscosity of 0.070-0.080, a T_g of 105°C, a GPC weight average molecular weight of 7,000-10,000, a GPC number average molecular weight of 2,500-4,000, and a polydispersity of 2.5-3.0, and ELVACITE 1020, a polymethylmethacrylate macromonomer having an inherent viscosity

of 0.085-0.10, a T_g of 105°C, a GPC weight average molecular weight of 12,000-15,000, a GPC number average molecular weight of 4,600-6,000, and a polydispersity of 2.5-3.0).

The copolymer preferably comprises between 60 and 93% by weight of units derived from A monomers and between 7 and 40% by weight of units derived from B monomers. More preferably, the copolymer comprises between 70 and 90% by weight of units derived from A monomers and between 10 and 30% by weight of units derived from B monomers. When present, units derived from macromers are preferably present in an amount between 1 and 7% by weight and more preferably in an amount between 2 and 5%.

The copolymer of the pressure sensitive adhesive composition of this invention can be prepared by conventional free radical polymerization of A and B monomers and optional further monomers and/or macromers. The polymerization can be a solution- or emulsion polymerization and can be a thermally or photochemically initiated polymerization. Useful free radical initiators are known in the art and include azo compounds, such as azo-bisisobutyronitrile and 4,4'-azobis(-4-cyanovaleric acid), hydroperoxides such as cumene, t-butyl and t-amyl hydroperoxide, dialkyl peroxides such as di-t-butyl and dicumylperoxide, peroxyesters such as t-butylperbenzoate and di-t-butylperoxy phtalate, diacylperoxides such as benzoyl peroxide and lauroyl peroxide. Preferably the copolymer obtained is soluble in ethyl acetate and has an inherent viscosity in the range 0.2 dl/g to about 1.8 dl/g, more preferably 0.6 dl/g to about 1.4 dl/g.

The drug is preferably present in the transdermal drug delivery device as free base and is present in a "therapeutically effective amount." The latter term means that the concentration of the drug is such that in the composition it results in a therapeutic level of drug delivered over the term that the dosage form is to be used. Such delivery is dependent on a great number of variables including, for example, the particular drug, the time period for which the individual dosage unit is to be used, and the flux rate of the drug from the system. The amount of drug needed can be experimentally determined. Generally, the drug is present in a device of the invention in an amount by weight of about 1 to about 25 percent, preferably about 4 to 15 percent, by weight based on the total weight of the adhesive layer. In a preferred embodiment the adhesive layer is substantially free of solid undissolved drug.

The adhesive layer can also contain agents known to accelerate the delivery of the drug through the skin. These agents have been referred to as penetration enhancers, accelerants, adjuvants, and sorption promoters, and are collectively referred to herein as "enhancers". Some examples of enhancers are polyhydric alcohols such as dipropylene glycol, propylene glycol, and polyethylene glycol; oils such as olive oil, squalene, and lanolin; polyethylene glycol ethers and fatty ethers such as cetyl ether and oleyl ether; fatty acid esters such as isopropyl myristate; fatty alcohols such as oleyl alcohol; urea and urea derivatives such as allantoin-; polar solvents such as dimethyldecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetonide, dimethylsulfoxide, decylmethylsulfoxide, and dimethylformamide and benzyl nicotinate. Examples of some particular agents include caprylic acid, eucalyptol, propanediol monolaurate, N-octyl-pyrrolidone, tocopheryl acetate, tocopheryl linoleate, propyl oleate, ethyl oleate, isopropyl palmitate, oleamide, polyoxyethylene (4) lauryl ether, polyoxyethylene (2) oleyl ether and polyoxyethylene (10) oleyl ether sold under the trademarks Brij 30, 93 and 97 by ICI Americas, Inc., and polysorbate 20 sold under the trademark Tween 20 by ICI Americas, Inc. It is furthermore possible to use a mixture of enhancers such as a mixture of caprylic acid and isopropyl myristate or a mixture of N-octyl-pyrrolidone and isopropyl myristate. Isopropyl myristate is particularly preferred in connection with this invention. Typically, the amount of enhancer used is between 5% by weight and 30% by weight and more preferably between 10% by weight and 25% by weight.

Further a plasticizer or tackifying agent can be incorporated into the adhesive composition to improve the adhesive characteristics of the adhesive composition. A tackifying agent is particularly useful in those embodiments in which the drug does not plasticize the polymer. Suitable tackifying agents are those known in the art including : (1) aliphatic hydrocarbons; (2) mixed aliphatic and aromatic hydrocarbons; (3) aromatic hydrocarbons; (4) substituted aromatic hydrocarbons; (5) hydrogenated esters; (6) polyterpenes; and (7) hydrogenated wood resins or rosins.

A transdermal delivery device in accordance with the invention can be prepared by dissolving the copolymer, optionally an enhancer such as isopropyl myristate and the drug in an organic solvent (e.g., ethyl acetate) to afford a coating formulation. The coating

formulation can be coated using conventional methods onto a suitable release liner to provide a predetermined uniform thickness of the coating formulation. Suitable release liners include conventional release liners comprising a known sheet material such as a polyester web, polyethylene web, or a polystyrene web, or a polyethylene-coated paper coated with a suitable fluoropolymer or silicone based coating. A preferred release liner is SCOTCHPAK™ 1022 film (3M).

The adhesive coated release liner is then dried and laminated onto a backing using conventional methods. The backing can be occlusive, non-occlusive or a breathable film as desired. The backing is flexible such that it conforms to the skin. It can be any of the conventional materials for pressure sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, high density polyethylene, randomly-oriented nylon fibers, polypropylene, ethylene-vinylacetate copolymer, polyurethane, rayon and the like. Backings that are layered, such as polyethylene-aluminum-polyethylene composites are also suitable. The backing should be substantially non-reactive with the ingredients of the formulation. Particularly preferred backings are SCOTCHPAK™ 1109 available from 3M and COTRAN™ 9722 available from 3M.

The transdermal delivery devices can be made in the form of an article such as a tape, a patch, a sheet, a dressing or any other form known to those skilled in the art. Generally the device will be in the form of a patch of a size suitable to deliver a preselected amount of the drug through the skin. Generally the device will have a surface area of about 10 cm^2 to about 100 cm^2 and preferably between 15 and 60 cm^2.

A transdermal delivery device in accordance with this invention containing as the drug tropisetron or granisetron can be used to treat any condition capable of treatment with these drugs and in particular the treatment of emesis and nausea and/or the prevention thereof. The device can be placed on the skin and allowed to remain for a time sufficient to achieve or maintain the intended therapeutic effect. The time that constitutes a sufficient time can be selected by those skilled in the art with consideration of the flux rate of the device of the invention and upon the condition being treated.

The examples set forth below are intended to illustrate the invention.

In Vitro Skin Penetration Test Method

The skin penetration data given in the examples below was obtained using the following test method. A static diffusion cell (Franz-cell type) is used. Hairless mouse skin (female hairless mice, 3-4 weeks old) or human skin (obtained from surgery) is used. The skin is mounted epidermal side up between the upper and the lower portion of the cell, which are held together by means of a ball joint clamp.

The portion of the cell below the mounted skin is completely filled with receptor fluid "HEPES" (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) buffered Hanks balanced salt solution, pH 7.2, supplemented with 4ml of anti-biotics (A 7292 obtained from Sigma) per liter such that the receptor fluid is in contact with the skin. The receptor fluid is stirred using a magnetic stir bar. The sampling port is covered except when in use.

When a transdermal delivery device is evaluated, the release liner is removed from a 1.55 cm^2 patch and the patch is applied to the skin and pressed to cause uniform contact with the skin and then the skin is placed across the orifice of the lower portion of the diffusion cell. The diffusion cell is assembled and the lower portion is filled with receptor fluid.

The cell is then placed in a constant temperature (32 ± 1.5°C) and humidity (45 ± 10% relative humidity) chamber. The receptor fluid is stirred by means of a magnetic stirrer throughout the experiment to assure a uniform sample and a reduced diffusion barrier on the dermal side of the skin. The entire volume of receptor fluid is withdrawn at specified time intervals (3, 6, 12, 24, 36 and 48 hours) and immediately replaced with fresh receptor fluid. The withdrawn receptor fluid is analyzed for drug content using conventional high performance liquid chromatography. The cumulative amount of drug penetrating the skin is calculated.

Stability test method

Drug containing patch formulations (10 cm^2 patches) were sealed in BAREX pouches and stored at the following two conditions:

25°C / 60 % relative humidity and 40°C / 75 % relative humidity

The patches were checked for their drug content before storage and after 2 and 4 weeks storage time. The drug content was determined by removing the liner from the patches and placing the remaining patch in a jar with a methanol/ethyl acetate mixture. Upon stirring over night the adhesive coating dissolved in the solvent mixture. After filtration of the solution an aliquot was taken and analysed for the drug content.

List of abbreviations:

IOA: iso-octylacrylate

NVP: N-vinyl-2-pyrrolidone

HEA: hydroxyethyl acrylate

IPM: isopropyl myristate

ELVACITE™: polymethylmethacrylate macromer available from ICI Acrylics

Preparation of the copolymers used in the examples.

Preparation of isooctyl acrylate/N-vinylpyrrolidone (91/9) copolymer

A flask equipped with an agitator, condensor, nitrogen inlet tube and an addition funnel is charged with isooctyl acrylate (91.0 g), N-vinylpyrrolidone (9.0 g) and ethylacetate (85 g). The mixture is heated to 60°C with medium agitation and purged with nitrogen to remove oxygen. 2,2'-Azobis-(2-methyl-butyronitrile) (0.1 g, Wako™ V-59) premixed in ethyl acetate (3.0 g) is added to initiate reaction. The reaction temperature is maintained at 60°C. Ethyl acetate (1.5 g) is added to the polymer solution every 30 minutes until the conversion of isooctyl acrylate to polymer reaches a minimum of 95%, typically 20-30 hours. An additional charge of 2,2'-azobis-(2-methyl-butyronitrile) (0.1 g) premixed with ethyl acetate is added after 5 hours and 9 hours

reaction time. The inherent viscosity in ethylacetate is measured by conventional means using a Canon-Fenske #50 viscosimeter in a water bath controlled at 27°C to measure the flow time of 10 millimeters of the polymer solution. The test procedure and apparatus are described in detail in „Textbook of Polymer Science", F.W. Billmeyer, Wiley Interscience, Second Edition, 1971, pages 84 and 85. The inherent viscosity was 1.62 dl/g.

Preparation of isooctylacrylate/N-vinylpyrrolidone/Elvacite™ 1020 (77/20/3) terpolymer

A flask equipped with an agitator, condensor, nitrogen inlet tube and an addition funnel is charged with isooctyl acrylate (134.75 g), N-vinylpyrrolidone (35.0 g) and Elvacite™ 1020 (5.25 g) premixed in a mixture of ethylacetate (236.25 g) and methanol (26.25 g). The mixture is heated to 60°C with medium agitation and purged with nitrogen to remove oxygen. 2,2'-Azobis-(2-methyl-butyronitrile) (0.26 g, Wako™ V-59) is added to initiate reaction. The reaction temperature is maintained at 57°C and the reaction is run for about 24 hours. After termination of the reaction additional ethyl acetate (90 g) and methanol (10 g) are added.

The inherent viscosity in ethyl acetate is measured by conventional means using a Canon-Fenske #50 viscosimeter in a water bath controlled at 27°C to measure the flow time of 10 millimeters of the polymer solution. The test procedure and apparatus are described in detail in „Textbook of Polymer Science", F.W. Billmeyer, Wiley Interscience, Second Edition, 1971, pages 84 and 85. The inherent viscosity was 1.4 dl/g.

Preparation of isooctylacrylate/hydroxyethylacrylate/Elvacite™ 1020 (59/39/2) terpolymer

This terpolymer was prepared similar to the procedure described above for isooctylacrylate/N-vinylpyrrolidone/Elvacite™ 1020. The inherent viscosity of the polymer in ethylacetate was 0.69 dl/g.

EXAMPLE 1

To 171.62 g of adhesive solution (IOA/NVP 91/9; 25% solid content) 3.474 g of tropisetron, 12.645 g IPM and 12 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 600µm and oven dried for 20 minutes at 60°C. The dried coating was then laminated with a backing (SCOTCHPAK™ 1109). The resulting device had a drug loading of 5.3 mg tropisetron per 10 cm^2. Samples of this device with a size of 1.55 cm^2 were tested with respect to the drug release/penetration characteristics through hairless mouse skin (HMS) and human cadaver skin (HCS). The cumulative amounts released after 24 hours were 303 $\mu g/cm^2$ via HMS and 308 $\mu g/cm^2$ via HCS. This corresponds to 57.2% and 58.1% of the initial drug loading, respectively. Stability testing of the formulations revealed chemical stability at 25 and 40°C for at least 4 weeks.

EXAMPLE 2

To 80.27 g of adhesive solution (IOA/NVP/ELVACITE™ 1020 (88/9/3); 24,3% solid content) 1.52 g of tropisetron, 5.75 g IPM and 5.43 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 620µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with either SCOTCHPAK™ 1109 or COTRAN™ 9722 backing. The resulting device had a drug loading of 5.7 mg tropisetron per 10 cm^2. Samples of these devices with a size of 1.55 cm^2 were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amounts released after 24 hours were 225.25 $\mu g/cm^2$ for the system with SCOTCHPAK™ 1109 and 219.17 $\mu g/cm^2$ for the system with COTRAN™ 9722. This corresponds to 39.52% and 38.45% of the initial drug loading, respectively. Stability testing of the formulations revealed chemical stability at 25 and 40°C for at least 4 weeks.

EXAMPLE 3

To 57.4 g of adhesive solution (IOA/NVP 91/9; 25% solid content) 1.15 g of tropisetron, 3.39 g IPM, 0.85 g N-octylpyrrolidone and 4 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved.

The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 600µm and oven dried for 20 minutes at 60°C. The dried coating was then laminated with a backing (SCOTCHPAK™ 1109). The resulting device had a drug loading of 6.3 mg tropisetron per 10 cm^2. Samples of this device with a size of 1.55 cm^2 were tested with respect to the drug release/penetration characteristics through hairless mouse skin (HMS) . The cumulative amount released after 24 hours was 373.57 $\mu g/cm^2$ via HMS. This corresponds to 59.3% of the initial drug loading.

EXAMPLE 4

To 50.16 g of adhesive solution (IOA/NVP/ELVACITE™ 1020 (77/20/3); 28.1% solid content) 0.99 g of tropisetron, 3.77 g IPM and 4.98 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 650µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 5.9 mg tropisetron per 10 cm^2. Samples of these devices with a size of 1.55 cm^2 were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amount released after 24 hours was 144.25 $\mu g/cm^2$. This corresponds to 24.46% of the initial drug loading.

EXAMPLE 5

To 50.36 g of adhesive solution (IOA/NVP/ELVACITE™ 1020 (77/20/3); 28.1% solid content) 0.95 g of tropisetron, 3.83 g IPM and 5.0 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 650µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 6.0 mg

tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amounts released after 24 hours was 112.90 µg/cm. This corresponds to 18.82 % of the initial drug loading.

EXAMPLE 6

To 50.45 g of adhesive solution (IOA/NVP/ELVACITE™ 1020 (77/20/3); 28.1% solid content) 0.84 g of tropisetron, 3.91 g IPM and 5.09 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (SCOTCHPAK™ 1022) at a wet thickness of 650µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 5.3 mg tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amount released after 24 hours was 88.0 µg/cm² for the system with SCOTCHPAK™ 1109. This corresponds to 16.6 % of the initial drug loading.

EXAMPLE 7

To 287.51 g of adhesive solution (IOA/HEA/ELVACITE™ 1020 (59/39/2); 39.2% solid content) 8.77 g of tropisetron, 31.77 g IPM and 30.0 g methanol were added. The solution was stirred at room temperature until all tropisetron was dissolved. The coating solution was coated onto a release liner (Daubert 164P) at a wet thickness of 400µm and oven dried for 20 minutes at 60°C. The dried coatings were then laminated with SCOTCHPAK™ 1109 backing. The resulting device had a drug loading of 5.7 mg tropisetron per 10 cm². Samples of these devices with a size of 1.55 cm² were tested with respect to the drug release/penetration characteristics through human cadaver skin (HCS). The cumulative amount released after 24 hours was 159.6 µg/cm² for the system with SCOTCHPAK™ 1109. This corresponds to 28.0% of the initial drug loading.

Stability testing of this formulation revealed a crosslinking of the drug-in-adhesive matrix and a decrease in the drug content of more than 10% within 4 weeks of storage.

CLAIMS

1. A transdermal drug delivery device comprising on a backing an adhesive layer, said adhesive layer comprising:

(a) a copolymer of one or more A monomers and one or more B monomers , said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said B monomers being hydrophilic monomers copolymerizable with said A monomers, and

(b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron.

2. A transdermal drug delivery device according to claim 1 wherein said B monomers are free of nucleophilic groups selected from the group consisting of hydroxy, thiol, primary amino groups, secondary amino groups and acid groups.

3. A transdermal drug delivery device according to claim 1 wherein said B monomers are selected from the group consisting of N-vinyl-2-pyrrolidone, vinylimidazoles, mono acrylates of poly(alkyleneoxide) alkyl ether, mono methacrylates of poly(alkyleneoxide) alkyl ether, acrylamides, N-vinyl valerolactam, N-vinyl caprolactam, vinyl acetate, tetra-alkylammonium containing monomers and tertiary amino group containing monomers.

4. A transdermal drug delivery device according to any of claims 1 to 3 wherein said copolymer is a copolymer of one or more A monomers and one or more B monomers and a macromer copolymerizable with the A and B monomers and said macromer having a weight average molecular weight between 500 and 500000.

5. A transdermal drug delivery device according to claim 4 wherein said macromer is selected from the group consisting of polymethylmethacrylate macromer, polymethylacrylate macromer, polystyrene macromer and polystyrene-acrylonitrile macromer.

6. A transdermal drug delivery device according to claim 4 wherein said copolymer comprises between 1 and 7% by weight of units derived from said macromer.

7. A transdermal drug delivery device according to any of the previous claims wherein said adhesive layer further comprises a penetration enhancer.

8. A transdermal drug delivery device according to any of the previous claims wherein said drug is substantially present as a free base in said adhesive layer.

9. A transdermal drug delivery device according to any of the previous claims wherein said copolymer comprises between 60 and 93 % by weight of units derived from A monomers and between 7 and 40% by weight of units derived from B monomers .

10. A transdermal drug delivery device according to any of the previous claims wherein said A monomers are selected from the group consisting of n-butyl, n-pentyl, n-hexyl, cyclohexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, isobornyl, 2-ethyloctyl, isooctyl, n-octyl and 2-ethylhexyl acrylates and methacrylates.

11. A pressure sensitive skin adhesive comprising :

(a) a copolymer of one or more A monomers and one or more B monomers , said A monomers being selected from the group consisting of alkylacrylates containing 4 to 12 carbon atoms in the alkyl group and alkylmethacrylates containing 4 to 12 carbon atoms in the alkyl group and said B monomers being hydrophilic monomers copolymerizable with said A monomers, and

(b) a therapeutically effective amount of a drug selected from the group consisting of tropisetron and granisetron.

12. A pressure sensitive skin adhesive according to claim 11 wherein said B monomers are free of nucleophilic groups selected from the group consisting of hydroxy, thiol, primary amino groups, secondary amino groups and acid groups.

13. A pressure sensitive skin adhesive according to claim 11 wherein said B monomers are selected from the group consisting of N-vinyl-2-pyrrolidone, vinylimidazoles, mono acrylates of poly(alkyleneoxide) alkyl ether, mono methacrylates of poly(alkyleneoxide) alkyl ether, acrylamides, N-vinyl valerolactam, N-vinyl caprolactam, vinyl acetate, tetra-alkylammonium containing monomers and tertiary amino group containing monomers.

14. A pressure sensitive skin adhesive according to any of claims 11 to 13 wherein said copolymer is a copolymer of one or more A monomers and one or more B monomers and a macromer copolymerizable with the A and B monomers and said macromer having a weight average molecular weight between 500 and 500000.

15. A pressure sensitive skin adhesive according to claim 14 wherein said macromer is selected from the group consisting of polymethylmethacrylate macromer, polymethylacrylate macromer, polystyrene macromer and polystyrene-acrylonitrile macromer.

16. A pressure sensitive skin adhesive according to claim 14 wherein said copolymer comprises between 1 and 7% by weight of units derived from said macromer.

17. A pressure sensitive skin adhesive according to any of claims 11 to 16 wherein the pressure sensitive skin adhesive further comprises a penetration enhancer.

18. A pressure sensitive skin adhesive according to any of claims 11 to 17 wherein said drug is substantially present as a free base.

19. A pressure sensitive skin adhesive according to any of claims 11 to 18 wherein said copolymer comprises between 60 and 93 % by weight of units derived from A monomers and between 7 and 40% by weight of units derived from B monomers .

20. A pressure sensitive skin adhesive according to any of claims 11 to 19 wherein said A monomers are selected from the group consisting of n-butyl, n-pentyl, n-hexyl, cyclohexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, isobornyl, 2-ethyloctyl, isooctyl, n-octyl, and 2-ethylhexyl acrylates and methacrylates.

21. A transdermal drug delivery device as claimed in any of claims 1 to 10 for use in the treatment of emesis or nausea or for the prevention of emesis or nausea.

22. Use of a pressure sensitive skin adhesive as claimed in any of claims 11 to 20 in the manufacture of a transdermal drug delivery device for use in the treatment or prevention of emesis or for use in the treatment or prevention of nausea.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 97/02842

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/415 A61K9/70

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical. search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document. with indication. where appropriate. of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 124, no. 20, 13 May 1996 Columbus, Ohio, US; abstract no. 270578, XP002054010 see abstract & JP 08 034 731 A (TEI TEI ESU GIJUTSU KENKYUSHO) 6 February 1996 ---	1-22
Y	WO 92 19226 A (DYNAGEN) 12 November 1992 see claims 1,3,5,6,43 ---	1-22
Y	WO 94 07468 A (CYGNUS) 14 April 1994 cited.in the application see the whole document ---	1-22
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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1

Date of the actual completion of theinternational search	Date of mailing of the international search report
30 January 1998	13/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office. P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 97/02842

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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